REMARKS

I. Status of the claims and support for the Amendment

Claims 2-4, 7, 10, and 14-17 are canceled by the instant amendment.

Claims 1, 5, 6, 8, 9, and 11 are currently amended.

Claims 1, 5, 6, 8, 9, and 11 are currently pending.

Amendment of the claims is fully supported by pages 7-9 of the specification.

Applicant explicitly reserves the right to pursue any canceled material in one or more continuation or divisional applications.

II. Information Disclosure Statement

The Examiner has alleged that the Tranchant reference (*M/S Medecine Sciences*, vol. 13, No. 8/09, August 1997) does not meet the requirements of 37 C.F.R. § 1.97 and § 1.98 because it is in French. The Examiner indicates that the reference has been placed in the file , but has not been considered as to the merits. In response, Applicant respectfully points out that page 997 of the Tranchant article (as originally submitted) provides an English summary of the article's contents.

With respect to the date of submission of the Tranchant reference, Applicant respectfully points out that the English summary was part of the original submission (on March 5, 2001) and was, therefore, timely filed within the requirements of 37 C.F.R. § 1.97(b). Accordingly, Applicant requests that the Tranchant article be considered on the merits to the extent of the English summary.

III. Priority

The Examiner has correctly indicated that the effective U.S. filing date for the instant application is 7 September 1999 (based on the filing date for international application PCT/EP99/06592). The Examiner has indicated that the priority date for the application is

7 September 1998, based on PCT/EP99/06592. This appears to be a typographical error. Applicant believes the correct priority date to be 8 September 1998, based on European application number 98870190.0 (*see* the first page of the PCT/EP99/06592 application).

III. Rejection of the Declaration

The Examiner has alleged that the Declaration is defective because it contains a hand-written correction (to the address of inventor Frank Hulstaert) which has not be initialed. In response, Applicant provides herewith a new Declaration executed by Frank Hulstaert. Applicant believes that with the submission of this Declaration, Applicant has fully complied with the requirements of 37 C.F.R. § 1.67(a). Accordingly, Applicant respectfully requests that the objection to the Declaration be withdrawn.

IV. Drawings

The drawings are objected to because "the lines corresponding to the '15' and '18' data sets in Figure 2 are not clearly drawn. In addition, the figure legend for Figure 2 is not decipherable." In response Applicant provides Formal Drawings herewith.

V. Rejection under 35 U.S.C. §112

A. Claims 1-3 and 5-11 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which is not described in the Specification so as to enable one of ordinary skill in the art to make and use the claimed invention. The Examiner specifically alleges that the Specification provides no guidance for:

1) A broad survey of the phosphorylated tau levels in normal or unaffiliated patients;
2) determining tau levels independent of phosphorylation;
3) non-ELISA methods of determining phosphorylated tau levels;
4) *in vivo* methods of determining tau levels, phosphorylated or not.

The Examiner goes on to assert that:

> The claimed invention is directed to an *in vitro* method for the early detection and/or quantification of CNS damage in an individual, which is not supported by the teachings of the specification or the prior art. One skilled in this art would be expected to reasonably doubt that the claimed method would work due to the following obstacles: Specificity of tau levels in association with any given neurological ailment or injury; How would [] a spinal tap (to remove CSF for assay) affect the patients; Are tau levels specific enough to warrant a specific course of treatment?; Expectation of success in finding "elevated" tau levels when all examples in the specification show a wide range of tau levels; Expectation of success in differentiating the myriad of causes that lead to elevated tau levels in CSF. The specification does not provide guidance on how to overcome expected obstacles. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure provided by the specification and the prior art for the following reasons.

(*see* pages 7-17 of the Office Action). Applicant respectfully traverses.

In response to point "1)" Applicant first of all wishes to stress that the present invention relates to the detection of all tau (also called "total tau"), that is any form of tau, including tau in any state of phosphorylation (this definition is provided at page 7, lines 14-15 of the specification). Accordingly, the present invention is directed to methods wherein, not only phosphorylated tau, but tau without abnormal phosphorylation is detected. This point is further emphasized in the specification at page 23, lines 6-8 (both normal and hyperphosphorylated tau is detected).

Further, Applicant notes that "a broad survey of the phosphorylated tau levels in normal or unaffiliated patients" is not the subject of the present invention. Rather, according to the instantly claimed invention total tau is detected. As indicated at page 23, lines 16-22, of the specification, determination of the range of tau levels characteristic for CSF samples from control healthy individuals is described. Tau levels were determined in six control CSF samples that were available. The obtained data were subsequently compared with data available in the literature. Furthermore, in view of the immorality of taking lumbar punctures from healthy

individuals without reason, the Specification cannot be expected to convey a broad survey on CSF-tau levels in normal or unaffiliated individuals.

With respect to point "2)", as discussed above, the present invention concerns the detection of total tau, *i.e.* any form of tau, including any state of phosphorylation. Accordingly, all examples in the application relate to the detection of tau, independent of phosphorylation.

With respect to point "3)", it is correct that the examples of the present invention use only and ELISA method for the detection of tau. However, the Specification (page 3, lines 22-27) clearly indicates that other methods for detecting tau were known in the art at the time the present application was filed. Further, Applicant wishes to emphasize that the present invention is drawn to the comparison of the CSF level of tau in individuals with brain damage relative to healthy individuals. Applicant argues that, absent evidence to the contrary, in such a comparison of tau levels the method by which the tau is detected is irrelevant so long as the same method is used for both groups (*i.e.* for analysis of tau in both healthy individuals and individuals with brain damage), allowing for a direct comparison of tau levels thereby determined.

With respect to point "4)", Applicant notes that, as currently amended, the present claims are drawn only to the detection of tau in cerebrospinal fluid (CSF).

In part 13 the Examiner alleges that one skilled in the art would be expected to reasonably doubt that the claimed method would work for the reasons listed by the Examiner. Applicant respectfully traverses.

Firstly, the Examiner has merely proffered the listed reasons. The Examiner provides no support to substantiate these allegations. In contrast, the Specification provides an ample disclosure and sufficient examples to fully enable the currently pending claims. Accordingly, in reliance upon the requirements of 37 C.F.R. § 1.104(d)(2), Applicant respectfully requests that

the Examiner provide specific facts to which Applicant can respond. If the facts are within the personal knowledge of the Examiner, Applicant requests that the Examiner provide an affidavit which sets out these facts and the support therefor, to which Applicant can respond.

As one alleged shortcoming, the Examiner contends that one skilled in the art would not expect the invention to "work" because the examples of the instant Specification show a wide range of tau levels (and no specific tau level is associated with a particular injury). In response, Applicant again stresses that the presently claimed invention is not drawn to a correlation between a certain neurological ailment or injury (*i.e.* cause of brain damage) and a particular level of tau. Rather, the present invention shows the correlation between the CNS damage caused in an individual by said neurological ailment or injury and the CSF level of tau in said individual. That is, it is the CNS damage (which can have a variety of causes), not its causative agent, which is the subject of the instantly claimed invention. Regardless of the cause, the result is the same: neuronal loss and an increase in CSF tau levels.

Accordingly, the CSF tau levels from individuals with the same neurological ailment or injury can vary widely if the level of CNS damage in said individuals is different. Conversely, the CSF levels from individuals suffering from different neurological ailments can be either the same or different, depending on the level of CNS damage in said individuals. Applicant asserts that the Specification provides sufficient data to support the assertion that the CSF-tau levels are not random, between patients, but that there is a correlation between CSF-tau levels and the degree of CNS damage. In support of this assertion Applicant provides the following:

1. Correlation: CNS invasion with CSF tau levels

a) Patients in which clear CNS invasion was detected showed CSF-tau levels above the cutoff value (312 pg/ml). See the examples cited in Table 1.

TABLE 1.

PATIENT	TAU LEVEL	EXAMPLE (in Specification)
1 patient with malignant cells in CSF	Increased	Example 1 (page 21, lines 9-11).
2 patients with over CNS invasion	Above 312 pg/ml	Example 2 (page 23, lines 26-27).
3 patients with increased intracranial pressure (caused by medulloblastoma)	823 pg/ml 1397 pg/ml 1500 pg/ml	Example 2 (page 23, line 30 through page 24, line 1).
1 patient with germinoma (tumor found in CNS)	422 pg/ml	Example 2 (page 23, line 30 through page 24, line 1).
1 patient with rhabdomyosarcoma stage IV (disease has metastasized)	320 pg/ml	Example 2 (page 24, lines 3-5).
1 patient with retinoblastoma and CNS involvement	1800 pg/ml	Example 2 (page 24, lines 5-6).

Thus, in all of the cases having documented CNS invasion, CSF-tau levels were substantially and consistently elevated above the cutoff level. If elevation of CSF-tau levels were a random phenomenon (*i.e.* not correlated with CNS invasion), CSF-tau levels would not have been elevated in all cases.

b) In contrast to the results in patients having CNS damage, it was observed that in patients with no CNS invasion (observed or expected), CSF-tau levels were normal, that is, below the cutoff level (*see*, Table 2).

TABLE 2.

PATIENT	TAU LEVEL	EXAMPLE (in Specification)
6 control children	106.2 pg/ml	Example 2 (page 23, lines 16-19).
1 patient with rhabdomyosarcoma stage I (no metastasis)	279 pg/ml	Example 2 (page 24, line 3-4).

Again, Applicant stresses that in all cases with no CNS invasion, CSF-tau levels were low (below the cutoff value). If elevated CSF-tau levels were a random phenomenon (*i.e.* not

correlated with CNS invasion), CSF-tau levels in individuals without CNS damage would not have been low in all cases.

c) As indicated the present invention is drawn to the *early* detection of CNS damage. In certain patients, where CNS invasion would be expected (*e.g.* by spread of the disease at a later pathological stage), elevated CSF-tau was found to be present, even though CNS invasion could not yet be detected by classical methods. It is believed that detectable invasion (by classical methods) would have been observed in these patients if the disease had been allowed to further progress. However, for ethical and humanitarian reasons, and obvious clinical reasons, these patients were treated to stop further progression of the invasion. Thus CNS invasion was not allowed to continue.

In view of the foregoing examples and arguments, Applicant believes that the Specification provides sufficient guidance to convince one of ordinary skill in the art that the instantly claimed invention is fully enabled. Specifically, these examples would convince the ordinarily skilled artisan that there is a clear correlation between CSF-tau levels and CNS damage (as caused by certain neurological ailments or injuries, as specified in claim 1). Accordingly, the skilled artisan would be persuaded that a "high" CSF-tau level measured in certain individual(s) (as specified in the claims) indicates that said individual(s) has/have suffered CNS damage. Furthermore, the ordinary skilled artisan would find a clear correlation between the level of CSF-tau measured with the degree of CNS damaged suffered by the individual.

Moreover, Applicant asserts that one of ordinary skill in the art would clearly understand that the level of CSF-tau does not correspond to any particular CNS malady or injury. Rather it correlates with the amount of CNS damage.

2. Correlation: size of infarction and CSF tau levels

The correlation between elevated CSF-tau levels and CNS damage was further substantiated by computerized tomography (CT) of the brains of patients with cerebral infarction (stroke). Figure 3 shows a clear correlation between the CSF-tau levels at maximum release and the size of the infarction, as measured by CT scan.

At part 14 of the Office Action, the Examiner alleges, in pertinent part, that the term "CNS damage" is viewed in the art as pertaining to a wide variety of injuries and disorders and that the claims are not enabled because they "fail to recite limitations for what constitutes applicable CNS damage," that there are not working examples directed to applicable forms of CNS damage and, therefore, undue experimentation would be required in order to allow the skilled artisan to make and use the claimed invention. Applicant respectfully traverses.

As described, above (in response to part 13.), the Specification does provide working examples. These working examples show a correlation between the CSF-tau levels and CNS damage caused by brain tumors, by brain metastasis, by invasion or metastasis of the CNS, by anoxia or ischemia, and by chemical agents. Accordingly, Applicant has restricted the claims to the detection of CNS damage caused by these injuries, agents, or diseases.

In part 15 of the Office Action, the Examiner makes allegations regarding "tumors" which are analogous to those made, regarding "injuries" in part 14. Applicant responds as follows.

In the context of "tumors" Applicant asserts arguments analogous to those made in response to part 14 of the Office Action. Firstly, the present Application is not drawn to a correlation between a certain type of brain tumor (which causes brain damage) and the level of CSF-tau. Rather, the instant specification demonstrates a correlation between the amount of

CNS damage in an individual, caused by the brain tumor, and the CSF-tau level in said individual.

Indeed for a number of primary brain tumors the Specification clearly shows the correlation between the CNS damage, caused by the primary brain tumor, and the level of CSF-tau (*see,* Table 3, below).

TABLE 3.

PRIMARY TUMOR	DEGREE OF TUMOR	TAU LEVEL	EXAMPLE
Grade I astrocytoma	Low grade	97 pg/ml	Example 2 (page 24, lines 1-2).
Germinoma	Tumor found in CNS	442 pg/ml	Example 2 (page 23, line 30 through page 24, line 1).
Medulloblastoma	Intracranial pressure	823 pg/ml 1397 pg/ml 1500 pg/ml	Example 2 (page 23, line 30 through page 24, line 1).
Retinoblastoma	With CNS involvement	1800 pg/ml	Example 2 (page 24, lines 5-6).

In view of the information presented above, Applicant contends that the Specification fully enables the instantly pending claims with respect to primary tumors.

Part 16 of the Office Action is analogous to parts 14-15, except that the rejection is based on the use of the term "hydrocephalus." Given that reference to "hydrocephalus" has been deleted from the claims as currently amended, this portion of the rejection is moot and should be withdrawn.

Part 17 of the Office Action is analogous to parts 14-16, except that the rejection is based on the use of the term "hematoma." Reference to "hematoma" has been deleted from the currently pending claims. Accordingly, this portion of the rejection is moot and should be withdrawn.

Part 18 of the Office Action is analogous to parts 14-17, except that the rejection is based on the use of the term "parasites." Reference to CNS damage caused by parasite derived cysts has been deleted from the claims as currently amended. Therefore, this portion of the rejection is moot and should be withdrawn.

Part 19 of the Office Action is analogous to parts 14-18. In this section of the Action the Examiner alleges that the Application contains insufficient working examples to enable the use of the term "invasion." The Examiner, therefore, alleges that the claims are not enabled by the Specification insofar as they are drawn to CNS damage caused by "invasion." Applicant respectfully traverses.

Applicant again argues similarly to the arguments made in response to parts 13. through 15. (specifically, that the present invention is not drawn to methods for correlating CSF-tau levels with any certain type of "invasion"). Rather, the present invention shows the correlation between the CNS damage caused in an individual by an invasion of the CNS and the CSF-tau level in said individual. Indeed, the examples provided in response to part 13. show that the CNS damage caused by a CNS invasion correlates with the level of CSF-tau. In view of these arguments, Applicant contends that the Specification fully enables the instantly pending claims with respect to the term "invasion."

Part 20 of the Office Action is analogous to parts 14-19 except that rejection of the claims is based on the use of the term "metastasis."

Again the present invention is not directed to a method for correlating certain tumor metastasis (as the cause of brain damage) with a particular level of tau. Rather, the instant invention shows the correlation between the CNS damage, caused in an individual by tumor metastasis, and the CSF-tau level in said individual. The Specification demonstrates a

correlation between CNS damage and CSF-tau levels for a number of tumor metastases (*see*, Table 4, below).

TABLE 4.

PRIMARY TUMOR	DEGREE OF TUMOR	TAU LEVEL	EXAMPLE
1 patient with rhabdomyosarcoma, stage I	Tumor has not metastasized	279 pg/ml	Example 2 (page 24, lines 3-4).
1 patient with rhabdomyosarcoma, stage IV	Tumor has metastasized	320 pg/ml	Example 2 (page 24, lines 3-5).
1 patient with Retinoblastoma	With CNS involvement	1800 pg/ml	Example 2 (page 24, lines 5-6).

In view of these arguments and examples, Applicant asserts that the Specification does provide sufficient enablement to support the use of the term "metastasis" in the currently pending claims. Accordingly, Applicant respectfully asserts that the instant rejection should be withdrawn, as it pertains to the use of the term "metastasis."

Part 21 of the Office Action is analogous to parts 14-20, except that the rejection is based on the use of the term "organisms." Reference to CNS damage caused by organisms has been deleted from the claims, as currently amended. Therefore, this portion of the rejection is moot and should be withdrawn.

Part 22 of the Office Action is analogous to parts 14-21 except that rejection of the claims is based on the use of the term "anoxia."

Applicant repeats that the instant invention is not drawn to a method of correlating a certain causative agent, anoxia, for example, (as a particular cause of brain damage) with particular level of tau. Rather, the instantly claimed invention is drawn to a method depending on the correlation between the CNS damage cased in an individual by a causative agent, such as

anoxia, and the CSF-tau levels in said individual. This correlation between CNS damage caused by anoxia and CSF-tau levels is demonstrated in the present application. Computerized tomography (CT) of the brain of patients with cerebral infarction (stroke) shows a clear correlation between the CSF-tau levels at maximum release and the size of the infarction (which is caused by anoxia), as measured by CT scan (*see* Figure 3). In view of the foregoing arguments and the example provided by the Specification, Applicant believes that the currently pending claims are fully enabled by the Specification. Accordingly, Applicant contends that the rejection of the claims, under 35 U.S.C. §112, first paragraph, should be withdrawn insofar as it pertains to the use of the term "anoxia."

Part 23 of the Office Action is analogous to parts 14-22 except that rejection of the claims is based on the use of the term "ischemia."

The instant invention is not related to a correlation between "ischemia" (as a certain cause of brain damage) and the level of tau. Rather the present invention shows the correlation between the CNS damage caused by ischemia in an individual and the CSF-tau levels in said individual. The correlation between elevated tau levels and CNS damage caused by ischemia is fully demonstrated in the present Application: computerized tomography (CT) of the brain of patients with cerebral infarction (stroke) shows a clear correlation between the CSF-tau levels at maximum release and the size of the infarction as measured by CT scan (*see* Figure 3). Accordingly, Applicant believes that the rejection of the claims under 35 U.S.C. §112, first paragraph, as it relates to "ischemia" has been overcome and should be withdrawn.

Part 24 of the Office Action is analogous to parts 14-23 except that rejection of the claims is based on the use of the term "agents." The Examiner alleges that the Specification

provides insufficient support to enable one of ordinary skill to make and use the invention, as claimed.

For this point, Applicant repeats that the claimed invention is related to a correlation between CNS damage and CSF-tau levels, not to a correlation between the presence of a certain causative agent (which produces brain damage) and CSF-tau levels. Applicant directs the Examiner's attention to Tables 1 and 2 of the Specification which describes the use of various chemical agents for the treatment of leukemia. The Specification also teaches how to measure tau in CSF (*see*, Example 2, pages 22-23 of the Methods section). Moreover, the Specification clearly teaches that elevated CSF-tau levels provide a measure of CNS damage caused by chemical agents (*see e.g.*, Specification page 6, lines 6-16 and page 9, lines 13-17).

Accordingly, Applicant asserts that the Specification provides ample guidance to enable one of ordinary skill in the art to detect CNS damage caused by chemical agents. Based on the instant Specification, the skilled person would know that a high CSF-tau level measured in an individual who has received chemical agents indicates that said individual has suffered CNS damage caused by the chemical agents. Further the skilled artisan would correlate the level of CSF-tau measured with the degree of CNS damage suffered by the individual.

Moreover, as currently amended the instantly pending claims are limited to chemical agents (as compared with other types of agents). In view of this amendment to the pending claims and in further view of the argument presented above, Applicant asserts that the rejection of the claims under 35 U.S.C. §112, first paragraph, as it pertains to agents has been overcome and should be withdrawn.

Part 25 of the Office Action is analogous to parts 14-24 except that rejection of the claims is based on the use of the terms "viral or bacterial encephalitis." Given that these terms are not present in the claims, as amended, this rejection is moot and should be withdrawn.

Part 26 of the Office Action is analogous to parts 14-25 except that rejection of the claims is based on the use of the terms "viral or bacterial meningitis." Given that these terms are not present in the claims, as amended, this rejection is moot and should be withdrawn.

Part 27 of the Office Action is analogous to parts 14-26 except that rejection of the claims is based on the use of the term "stroke."

Applicant repeats that the present invention concerns a correlation between CNS damage and CSF-tau levels, not a correlation between CSF-tau levels and a certain instance of stroke (*i.e.* the cause of the brain damage). The instant Specification clearly demonstrates the correlation between elevated CSF-tau levels and the CNS damage caused by stroke. Computerized tomography of the brains of patients with cerebral infarction (stroke) shows a clear correlation between the CSF-tau levels at maximum release and the size of the infarction as measured by CT scan (*see* Figure 3). In view of these facts, Applicant has demonstrated that the Specification fully enables the currently pending claims with respect to recitation of the term "stroke." Accordingly, applicant respectfully requests that the rejection of the claims under 35 U.S.C. §112, first paragraph, as it pertains to the use of the term "stroke" be withdrawn.

Parts 28 and 29 of the Office Action are analogous to parts 14-27 except that the rejection of the claims is based on the use of the terms "pharmaceuticals" and "chemotherapy," respectively. In view of the arguments presented in response to Part 24 of the Office Action, Applicant contends that the rejections set out in Parts 28 and 29 have been overcome and should be withdrawn.

Part 30 of the Office Action is analogous to parts 14-29 except that rejection of the claims is based on the use of the term "radiation." As currently amended the instantly pending claims no longer recite the offending term. Accordingly, rejection based on use of the term "radiation" is moot and should be withdrawn.

Part 31 of the Office Action is analogous to parts 14-30 except that the rejection of the claims is based on the use of the term "treatment." As noted the presently claimed invention is not directed to a correlation between CSF-tau levels and any particular "treatment." Rather, the instantly claimed invention is directed to Applicant's discovery of the correlation between CNS damage (which may be caused by various "treatments") and elevated CSF-tau levels. In view of the arguments presented in response to Part 24 of the Office Action, Applicant contends that the rejection set out in Part 31 has been overcome and should be withdrawn.

In Part 32 of the Office Action the Examiner alleges that "the application must establish a nexus between the tau levels recited in the claims for each form of CNS damage and a measurable, significant change in tau levels recited in the case." Applicant respectfully traverses.

As Applicant has discussed above, the purpose of the instant invention (as the language of the currently pending claims clearly shows) is not to establish a nexus between tau levels and each particular cause of CNS damage. Rather the aim of the instant invention, as stated in the claims, as amended, is to establish a nexus between CNS damage and CSF-tau levels, independent of the cause of the CNS damage. The instant Specification establishes this nexus or correlation for CNS damage caused by primary brain tumors, by brain metastasis, by invasion or metastasis of the CNS, by anoxia or ischemia, and by chemical agents.

Therefore, the instant Specification provides clear guidance that would enable and artisan of ordinary skill in the art to determine the presence or absence of CNS damage, by measuring the CSF-tau levels. Furthermore, a skilled artisan would clearly interpret an elevated CSF-tau level in a patient known to have (or potentially have) one of the causative agents described above (*e.g.* stroke, ischemia, or metastasis) as indicating that the patient has suffered CNS-damage induced by the causative agent.

The Examiner further alleges that "the tau as measured in patients was phosphorylated not absolute levels of tau in the spinal cord or the brain *per se*." Applicant respectfully traverses. As noted on page 23 of the Specification (*see* lines 1-12), the Specification clearly teaches that the tau measured is total tau (*i.e.*, both normal and hyperphosphorylated tau).

The Examiner also alleges that "tau appears to be elevated in a broad range of neurological traumas and not necessarily associated with any particular stage of the trauma, disease, or disorder, whether early or not." Applicant respectfully traverses.

Firstly, as explained in response to Part 13 of the Office Action, the instant Specification clearly shows a correlation between the degree of CNS damage and CSF-tau level. Furthermore, as explained, the instant invention is not intended to show a correlation between any particular disorder.

With respect to the term "early," as used in the claims Applicant notes that "early detection" is defined at page 7, lines 10-13 of the Specification, which recites that "'[e]arly detection and/or quantification of CNS damage' means that the CNS damage is determined by a method that allows it to be detected before it is detectable by the current methods."

As was elaborated in response to Part 13 of the instant Office Action, the Specification provides examples of each of the following:

a) The detection of high CSF-tau levels in patients with CNS damage (where the CNS damage is also detectable by other methods available at the time the application was filed).

b) The detection of low CSF-tau levels in patients where no CNS damage is either known or expected to exist (and which is not detectable by other available methods).

c) The detection of high CSF-tau levels in patients where CNS invasion could be expected to occur (*e.g.* in a disease where CNS damage is expected as the disease progresses), but which is not yet detectable by classical means. Applicant notes that it would have been possible to detect the CNS damage by classical methods if the disease had been allowed to progress (to confirm Applicant's observations). However, it would have been both unethical and clinically imprudent to allow the invasion to progress to such a more advanced stage. Therefore, once an elevated CSF-tau level was detected, the patients were treated to prevent further invasion, and, thereby, prevent additional CNS damage.

Applicant notes that the Examiner has cited a number of references in support of the rejections made in Part 32 of the Office Action. Applicant asserts that none of the cited publications controverts Applicant's position. That is none of the cited references teaches or suggests that there is no correlation between CNS damage and elevated CSF-tau levels. Moreover, none of the cited references contradict Applicant's assertions by teaching or suggesting that CSF-tau levels vary randomly. Applicant addresses each reference in turn.

- Arvanitakis and Wszolek, 2001: This paper is drawn primarily to mutations in tau. It provides no teachings regarding CSF-tau levels.
- Kapaki *et al.*, 2000: This publication reports on the measurement of the CSF-tau levels in patients suffering from multiple sclerosis (MS). It concludes (*see* abstract, last sentence) that the CSF-tau data may indicate axonal impairment in MS patients and that these data may provide a tool for the estimation of axonal damage during life. Accordingly, this publication (published well after the priority date for the present application), comes to the same conclusion as the instant Application (*i.e.*, that there is a correlation between CSF-tau levels and CNS damage (specifically with respect to MS).
- Spillantini and Goedert, 1998: This publication makes no reference to CSF-tau levels.

- Molina *et al.*, 1997: This publication reports on the measurement of CSF-tau levels in patients suffering from Parkinson's disease (PD), without dementia. According to the reference, the CSF-tau levels in these patients were not elevated. The publication draws no conclusions as to CNS damage in these patients. The paper concludes only that CSF-tau levels were not elevated and seem to be unrelated to risk for PD.
- Ellis *et al.*, (18 Sept. 1998): This publication reports on the measurement of the CSF-tau levels in HIV-associated neurological disease. CSF-tau levels in HIV-associated neurological disease were not elevated. The authors conclude that HIV-associated neurological disorders might be consistent with less severe neurological loss (*see*, page 4, left-hand column, last full paragraph). Accordingly, this article (published after the priority date for the instant application) can be viewed as suggesting that high CSF-levels might be correlated with CNS damage.
- Bitsch *et al.*, 2002: The work described in this publication relates to tau levels in serum. It does not address CSF-tau levels as they pertain to CNS damage other than to recite that "tau protein...is elevated in the cerebrospinal fluid of patients with neurodegenerative disease" (*see*, the abstract).
- Süssmuth *et al.* 2001: This publication describes a study of CSF- tau levels in patients with bacterial meningitis and MS. Moreover, the conclusions of the paper support Applicant's position that elevated CSF-tau correlates with CNS damage. Specifically, this paper concludes, *inter alia*, that elevated CSF-tau levels in patients with bacterial meningitis indicated that there were encephalitic complications and that an elevated CSF-tau level is associated with clinically active MS (axonal damage) (*see*, page 98, left column). Thus, the conclusions of this paper are fully consistent with the position taken by Applicant in the current Application.
- Galasko, 2001: This paper relates to the use of CSF-tau as a biomarker for Alzheimer's disease (AD). It states that CSF-tau may be increased with other disorders. This publication makes no comment regarding a correlation between CSF-tau and CNS damage.

- Pilkington *et al.*, 1997: This publication is directed to a discussion of various *in vitro* and *in vivo* models for the study of brain invasion. The publication provides no discussion of CSF-tau measurements.
- Dengler, *et al.*, 1998: This publication describes a retrospective analysis of the CSF profile of patients diagnosed with Kawasaki disease. However, the paper provides no indication that CSF-tau levels were evaluated.
- Zhang and Tuomanen, 1999: This is a review article which discusses the molecular and cellular mechanisms for microbial entry into the CNS. The publication provides no discussion of CSF-tau levels.

In summary, Applicant has shown that the instantly pending claims are fully enabled by the Specification. In doing so Applicant has demonstrated that the instant invention is related to the correlation between CNS damage and elevated CSF-tau levels. Specifically, the Specification teaches that patients suffering from CNS damage produced by one of the causative agents recited in the currently pending claims, have elevated CSF-tau levels (*i.e.*, elevated as compared with CSF-tau levels in normal patients). Further, Applicant has explained that the instant invention is not intended to provide a means of identifying any particular agent as causing the CNS damage. Rather, the instantly claimed invention serves as a means to aid in the early detection of CNS damage. Finally, Applicant has demonstrated that none of the references cited by the Examiner provide any teaching or suggestion that refutes or even weakens Applicants assertions. On the contrary, those references that address, even tangentially, the matter of CSF-tau levels and CNS damage support the Applicant's position.

In view of the claim amendments and the arguments presented above, Applicant believes that all rejections of the currently pending claims under 35 U.S.C. §112, first paragraph, have been overcome. Consequently, Applicant respectfully requests that these rejections be withdrawn.

B. Claims 1-3 and 5-11 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. The Examiner asserts that the "claims do not recite what result is required to achieve the goals set forth in the preambles. Thus the claims are incomplete." Applicant respectfully traverses.

As currently amended claim 1 (and all other claims as depending therefrom) now recite the result(s) required to achieve the goal(s) set forth in the claim preambles. Accordingly, Applicant believes that the rejection of the claims under 35 U.S.C. §112, second paragraph, has been overcome and should be withdrawn.

VI. Rejection under 35 U.S.C. §102

Claims 1-3 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Pat. No. 5601985 (Troganowski *et al.*, hereinafter, the '985 patent). In rejecting the instant invention the Examiner alleges that:

> US 5601985 teaches a method of detecting tau levels in cerebrospinal fluid using a monoclonal antibody thus meeting the limitations of claims 2 and 3 (claims 1-4). US 5601985also describes a method of detecting the level of tau in the cerebrospinal fluid of AD patients, patients with non-AD neurological disease, and normal patients using an ELISA assay thus meeting the limitations of claims 1, 2, and 3 (FIG. 4; Col. 7 lines 55-67, Col. 8 lines 1-21). The phrase "for early detection..." is an intended use and is not afforded patentable weight in accordance with case law. US 5601985 teaches the method steps (1) determining the level of tau in an individual with the recited CNS damage, (2) comparing it to the level of tau in control healthy individuals. Since US 5601985 discloses the method steps it is fully anticipatory. Thus US 5601985 anticipates claims 1, 2, and 3.

Applicant respectfully traverses.

The MPEP chapter 2100 sets out the requirements for establishing anticipation under 35 U.S.C. §102. *MPEP* §2131 recites, *inter alia*, that:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a singly prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 2 USPQ2d

1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Applicant asserts that the '985 patent does not meet these requirements with respect to the currently pending claims. Firstly, the instantly pending claims now specifically recite the steps necessary for a method of the detection of CNS damage. The '985 patent does not set forth the necessary elements. Namely, it does not teach, either explicitly or implicitly, a method for detecting CNS damage. Secondly, the '985 patent teaches and claims the use of antibodies to detect an "abnormally phosphorylated" tau. In contrast, as has been described above, the instant claims are drawn to methods which comprise the detection of all tau (both normal and hyperphosphorylated). Thus, the '985 patent fails to teach at least two elements of the instantly pending claims.

In view of the claim amendments and the foregoing arguments, Applicant asserts that the rejection of the claims under 35 U.S.C. §102(b) has been overcome and should be withdrawn.

VII. Conclusions

In view of the amendment of the claims, the arguments presented above, the new Declaration, and the formal drawings provided herewith, Applicant believes that all objections to and rejections of the claims and specification have been overcome and should be withdrawn. Consequently, Applicant respectfully requests favorable reconsideration of the instant Application and issuance of a Notice of Allowance therefor.

The Examiner is invited to contact the undersigned patent agent at (713) 787-1589 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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